VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

The sentence beginning at line 26 of page 33 has been amended as follows.

Various combinations of these ten resulting *M. tuberculosis* antigen recombinant WRG7054 plasmid constructs were used to [from] form cocktail compositions for the vaccination study.

The sentence beginning at line 28 of page 33 has been amended as follows.

M. tuberculosis H37Rv and *M. bovis* BCG Pasteur cultures ([Copenhaga] Copenhagan 1331) were obtained from a commercial source, grown to early mid-log phase, and aliquots were stored at -70°C until used.

In the Claims:

Claims 9, 12, 17, 20, 31, 34, 43 and 46 have been deleted without prejudice and disclaimer.

Claims 7, 10-11, 13, 15, 18-19, 21, 25-26, 32-33, 35, 37, 44-45 and 47 have been amended as follows.

7. (Amended) A method for eliciting an immune response against *M. tuberculosis* in a subject, said method comprising:

(a) obtaining a vector construct that has inserted therein a recombinant polynucleotide containing a plurality of *Mycobacterium tuberculosis* antigens operably linked to control sequences suitable for expression in the subject; and

(b) administering said vector construct to the subject [a vector according to claim 2] whereby said antigens are expressed in the subject at sufficient levels to elicit an immune response.

10. (Amended) The method of claim [9] 8, wherein the secondary composition comprises at least one [protein antigen comprises] culture filtrate [proteins] protein antigen of *M. tuberculosis*.

11. (Amended) The method of claim [9] 8, wherein the secondary composition comprises at least one [protein antigen comprises] isolated [subunits] subunit of a *M. tuberculosis* [proteins] protein.

13. (Amended) The method of claim [12] 8, wherein the secondary composition comprises a live attenuated vaccine [is] derived from a [*M. tuberculosis*] *Mycobacterium* species.

15. (Amended) A method for eliciting an immune response against *M. tuberculosis* in a subject, said method comprising:

(a) obtaining a composition containing a plurality of recombinant polynucleotides each comprising a sequence encoding a *Mycobacterium tuberculosis* antigen operably linked to control sequences suitable for expression in the subject; and

(b) administering the composition to the subject [a composition according to claim 5] whereby each said antigen is expressed in the subject at sufficient levels to elicit an immune response.

18. (Amended) The method of claim [17] 16, wherein the secondary composition comprises at least one [protein antigen comprises] culture filtrate [proteins] protein antigen of *M. tuberculosis*.

19. (Amended) The method of claim [17] 16, wherein the secondary composition comprises at least one [protein antigen comprises] isolated [subunits] subunit of a *M. tuberculosis* [proteins] protein.

21. (Amended) The method of claim [20] 16, wherein the secondary composition comprises a live attenuated vaccine [is] derived from a [*M. tuberculosis*] *Mycobacterium* species.

25. (Amended) A method for eliciting an immune response to *M. tuberculosis* in a subject, said method comprising:

(a) providing a core carrier coated with a [composition according to claim 2] vector construct that has inserted therein a recombinant polynucleotide containing a plurality of *Mycobacterium tuberculosis* antigens operably linked to control sequences suitable for expression in the subject; and

(b) administering the coated core carrier to the subject using a particle-mediated delivery technique, wherein the *M. tuberculosis* antigens are expressed in the subject at sufficient levels to elicit an immune response.

26. (Amended) The method of claim 25, wherein [thecore] the core carrier has an average diameter of about 0.5 to about 5 μm and a density sufficient to allow delivery into the subject.

32. (Amended) The method of claim [31] 30, wherein the secondary composition comprises at least one [protein antigen comprises] culture filtrate [proteins] protein antigen of *M. tuberculosis*.

33. (Amended) The method of claim [31] 30, wherein the secondary composition comprises at least one [protein antigen comprises] isolated [subunits] subunit of a *M. tuberculosis* [proteins] protein.

35. (Amended) The method of claim [34] 30, wherein the secondary composition comprises a live attenuated vaccine [is] derived from a [*M. tuberculosis*] *Mycobacterium* species.

37. (Amended) A method for eliciting an immune response to *M. tuberculosis* in a subject, said method comprising:

(a) providing a core carrier coated with a [vector according to claim 5] composition containing a plurality of recombinant polynucleotides each comprising a sequence encoding a *Mycobacterium tuberculosis* antigen operably linked to control sequences suitable for expression in the subject; and

(b) administering the coated core carrier to the subject using a particle-mediated delivery technique, wherein the *M. tuberculosis* antigens are expressed in the subject at sufficient levels to elicit an immune response.

44. (Amended) The method of claim [43] 42, wherein the secondary composition comprises at least one [protein antigen comprises] culture filtrate [proteins] protein antigen of *M. tuberculosis*.

45. (Amended) The method of claim [43] 42, wherein the secondary composition comprises at least one [protein antigen comprises] isolated [subunits] subunit of a *M. tuberculosis* [proteins] protein.

47. (Amended) The method of claim [46] 42, wherein the secondary composition comprises a live attenuated vaccine [is] derived from a [*M. tuberculosis*] *Mycobacterium* species.

REMARKS

Introductory Comments:

Claims 1-55 were pending in the application. Applicants note with appreciation that the Office has acknowledged applicants' election of Group II, claims 7-49, as provided for in the Response filed 28 August 2001. As a result, claims 1-6 and 50-55 have been withdrawn from further consideration pursuant to 37 C.F.R. § 1.142(b) as drawn to a non-elected invention.

Accordingly, claims 7-49 are currently under consideration and were examined in the Office Action dated 20 November 2001. In the Action, the drawings, specification and claims were objected to on the basis of informality. In addition, the Office has asserted the following claim rejections: **(1)** claims 8, 9, 12, 16, 17, 20, 30, 31, 34, 42, 43 and 46 stand rejected under 35 U.S.C. § 112, second paragraph, as indefinite; **(2)** claims 37-49 stand rejected under 35 U.S.C. § 112, second paragraph, on the basis of antecedence; **(3)** claims 13, 14, 21, 22, 35, 36, 47 and 48 stand rejected under 35 U.S.C. § 112, second paragraph, as indefinite; **(4)** claims 7-49 stand rejected under 35 U.S.C. §112, first paragraph, as nonenabled; **(5)** claims 8-13, 16-21, 30-35 and 42-47 stand rejected under 35 U.S.C. § 112, first paragraph, as nonenabled; **(6)** claims 7-11 and 15-19 stand rejected under 35 U.S.C. §103(a) as unpatentable over Lowrie et al. (1997) *Vaccine* 15(8):834-838 ("Lowrie"); and **(7)** claims 23, 25-33 and 37-45 stand rejected under 35 U.S.C. §103(a) as unpatentable over the combination of Lowrie in view of U.S. Patent No. 5,100,792 to Sanford et al. ("Sanford"). All objections to the specification, figures and the claims, and all claim rejections are traversed for the following reasons.

Overview of the Amendment:

Applicants, by way of this response, have entered amendments to the specification and the claims. More particularly, two minor amendments have been made to the specification at page 33, both to correct obvious typographical errors as helpfully pointed out by the Office. In one sentence, the word "from" has been replaced with the word "form" as obviously intended by reference to the rest of the sentence. In another sentence, a typographical error has been corrected to the name "Copenhagan." Accordingly, no new matter has been added to the specification by way of these amendments, and the entry thereof is respectfully requested.

Claims 9, 12, 17, 20, 31, 34, 43 and 46 have been cancelled without prejudice and disclaimer. It is to be understood that cancellation of these claims is not meant to be an acquiescence to any rejection raised in the application, and applicants expressly reserve the right to bring the claims again in a subsequent, related application. In addition, claims 7, 10-11, 13, 15, 18-19, 21, 25-26, 32-33, 35, 37, 44-45 and 47 have been amended. More particularly, claims 7 and 25 have been amended to incorporate the limitations from (nonelected) claims 1 and 2 upon which they originally depended. Claims 7 and 25 thus now expressly recite the vector construct containing a recombinant polynucleotide with antigens operably linked to control sequences. Support for these amendments can be found in claims 1, 2, 7 and 25 as originally filed and throughout the specification at, for example, page 10, lines 12-17 (vector construct); page 11, lines 13-19 and page 14, lines 17-20 (recombinant polynucleotide); and page 11, lines 5-12 and page 17, lines 8-12 (operably linked). Claims 15 and 37 have been amended to incorporate the limitations from (nonelected) claim 5 upon which they originally depended. Claims 15 and 37 thus now expressly recite the composition multiple recombinant polynucleotides each containing an antigen operably linked to control sequences. Support for these amendments can be found in claims 5, 15

and 37 as originally filed and throughout the specification at, for example, page 11, lines 13-19 and page 14, lines 17-20 (recombinant polynucleotide); and page 11, lines 5-12 and page 17, lines 8-12 (operably linked). Claims 10, 18, 32 and 44 have been amended to correct their dependence from (now deleted) earlier claims, and to more clearly recite that the secondary composition contains a culture filtrate protein antigen from *M. tuberculosis*. Support for these amendments can be found in claims 10, 18, 32 and 44 as originally filed and throughout the specification. Claims 11, 19, 33 and 45 have been amended to correct their dependence from (now deleted) earlier claims, and to more clearly recite that the secondary composition contains isolated protein subunits from *M. tuberculosis*. Support for these amendments can be found in claims 11, 19, 33 and 45 as originally filed and throughout the specification. Claims 13, 21, 35 and 47 have been amended to correct their dependence from (now deleted) earlier claims, and to more clearly recite that the secondary composition contains a live attenuated vaccine derived from a *Mycobacterium* species. Support for these amendments can be found in claims 13, 21, 35 and 47 as originally filed and throughout the specification. Finally, claim 26 has been amended to correct an obvious typographical error as helpfully pointed out by the Office. Accordingly, no new matter has been added by way of these claim amendments, and the entry thereof is respectfully requested.

A marked-up version of the changes made to the specification and claims by the current amendment is attached and appears herein above. The attached page is captioned "Version With Markings to Show Changes Made."

The Objections to the Specification, Figures and Claims:

The Office has indicated that the drawings submitted with the application are acceptable for examination purposes only, where a number of

informalities have been pointed out in an attached form PTO-948. Applicants acknowledge receipt of the objections, and will submit amended drawings once agreement has been reached on allowable subject matter.

The specification was objected to as informal on the basis of typographical errors appearing in two different sentences on page 33. Correction was required. Applicants draw the Office's attention to the amendments to the specification tendered herewith, whereby the errors have now been corrected. Reconsideration and withdrawal of the objection to the specification is thus respectfully requested.

The specification was also objected under 37 C.F.R. §1.821(d) on the basis that sequences appear in the specification or claims without use of a sequence identifier preceded by "SEQ ID NO:". Applicants have carefully examined the specification as filed and note that the only sequences appear on pages 31 and 32 and that all such sequences are clearly marked with a sequence identification number. Clarification of the basis for the objection is thus requested should the Office wish to maintain the instant ground of objection.

Claims 7-49 were objected to as informal on the basis that all claims depend from nonelected claims 1, 2 and 5. Correction was required. In response, applicants draw the Office's attention to the claim amendments tendered herewith, whereby all claim dependencies have now been corrected. Reconsideration and withdrawal of the objection is thus respectfully requested.

Claim 26 was object to as informal on the basis of the term "thecore" that appeared therein. Here again, applicants draw the Office's attention to the amendment to claim 26 tendered herewith, whereby this obvious typographical error has been corrected. Reconsideration and withdrawal of the objection to claim 26 is thus respectfully requested.

The Rejections under 35 U.S.C. §112, second paragraph:

Claims 8, 9, 12, 16, 17, 20, 30, 31, 34, 42, 43 and 46 stand rejected under 35 U.S.C. §112, second paragraph, as indefinite. In particular, the Office has objected that the "secondary composition" recited therein is indefinite. Initially, applicants draw the Office's attention to the claim amendments wherein claims 9, 12, 17, 20, 31, 34, 43 and 46 have been deleted, rendering the rejection of those claims moot. Applicants traverse the remaining rejection of claim 8 on the basis that "boosting step" recited therein (with the "secondary composition") is indeed clear from a proper reading of the specification and accompanying working examples. Reconsideration and withdrawal of the rejection of claim 8 under 35 U.S.C. §112, second paragraph, is thus respectfully requested.

Claims 37-49 stand rejected under 35 U.S.C. §112, second paragraph, as indefinite on the basis that there is insufficient antecedent basis for the limitation "vector according to claim 5"appearing in claim 37. In response, applicants draw the Office's attention to claim 37 as now amended wherein the subject antecedence has been corrected. Reconsideration and withdrawal of the rejection of claims 37-49 under 35 U.S.C. §112, second paragraph, is thus respectfully requested.

Claims 13, 14, 21, 22, 35, 36, 47 and 48 stand rejected under 35 U.S.C. §112, second paragraph, as indefinite. With regard to claims 13, 21, 35 and 47, the Office notes that the recitation that the "live attenuated vaccine is derived from a *M. tuberculosis* species" is unclear since "*M. tuberculosis* is itself a species." Office Action at page 4. With regard to claims 14, 21, 22, 36 and 48, the Office objects that recitation that "the live attenuated vaccine derived from a *M. tuberculosis* species" is unclear since BCG is an attenuated form of *M. bovis*. In response, applicants draw the Office's attention to the amendments to the claims whereby the above-noted issues have been corrected by the clarifications entered into those claims. Reconsideration and

withdrawal of the rejection of claims 13, 14, 21, 22, 35, 36, 47 and 48 under 35 U.S.C. §112, second paragraph, is this respectfully requested.

The rejections under 35 U.S.C. §112, first paragraph:

Claims 7-49 stand rejected under 35 U.S.C. §112, first paragraph, as nonenabled. In particular, the Office has raised a series of scope of enablement issues since the Office has acknowledged that applicants have enabled numerous embodiments encompassed by the claims.

Initially, the Office asserts that the specification, "while enabling for a composition comprising individual specific vectors comprising individual specific DNA encoding specific *M. tuberculosis* antigens, does not reasonably provide enablement for any and all other combinations of ... antigens in a single vector." Office Action at page 5. The Office then goes on to discuss the so-called Wands factors in support of its assertion, pointing out that the working examples used various combinations of single antigen constructs. Office Action at page 6. On this basis alone, the Office asserts that the skilled artisan would need to practice undue experimentation to make and use the invention as claimed. Applicants respectfully traverse.

Applicants' burden under Section 112 is merely to provide a specification that enables a person reasonably skilled in the art to make and use the claimed invention without undue experimentation. The fact that some experimentation may be employed, however, does not make it undue if a person of skill in the art typically engages in such experimentation. This is because the prohibition is against "undue experimentation," not merely "experimentation." *In re Angstadt*, 190 USPQ 214 (CCPA 1976).

Applicants have provided a detailed disclosure of the antigens to be used in the methods of the invention, where to find the sequence information for such antigens, how to go about obtaining the sequences, how to select appropriate control sequences, how operably link antigen sequences to control

sequences to obtain an expression cassette, how to insert the expression cassettes into numerous different vector systems, and how to administer these various vector systems to obtain expression of the antigens of interest. See applicants' specification at pages 14-20. Although not required under Section 112 (*In re Robbins*, 166 U.S.P.Q. 552 (CCPA 1970)), applicants have exemplified their thoroughly enabling disclosure with a number of working examples using, for convenience, a series of single antigen vectors so as to facilitate screening of a large number of different antigen combinations.

The Office has now asserted that the skilled artisan would somehow be unable to take the enabling disclosure that has been provided by applicants, and apply it to vector systems containing more than one antigen. There is no technical or scientific basis for this assertion, just the bald statement that producing the multi-antigen constructs would require undue experimentation. For this reason, the Office has failed in its burden to establish a *prima facie* showing of nonenablement. This is because the determination of whether or not something is indeed undue experimentation must be judged by the standards of those skilled in the art. Applicants submit that, given the level of skill in the art, the detailed description provided by the specification, and the numerous working examples, a skilled artisan could readily practice the claimed invention without undue experimentation. See, e.g., *Utter v. Hiraga*, 6 USPQ2d 1709, 1714 (Fed. Cir. 1988), and *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, 94 (Fed. Cir. 1986).

Applicants have provided more than sufficient disclosure regarding how to make and use their recited compositions, and has exemplified this disclosure with express working examples. The skilled artisan would thus have no difficulty in following applicants' directions to test other, multi-antigen compositions for their ability to induce an immune response in a suitable subject. Although some experimentation may need to be carried out, the mere fact that some experimentation may be required to practice the

invention throughout its entire scope does not necessarily make it "undue," particularly when the level of skill in the art is typically high, and such experimentation is routinely carried out. It is well settled that satisfaction of the enablement requirement of Section 112 is not precluded by the necessity for some experimentation such as routine screening.

Accordingly, the rejection of claims 7-49 under 35 U.S.C. §112, first paragraph, is improper and simply not supported by any evidence of record in the case. Reconsideration and withdrawal of the rejection is thus earnestly solicited.

The Office next asserts that the specification, "while enabling for alterations in weight, bacterial load, and tissue pathology in guinea pigs, does not reasonably provide enablement for eliciting an immune response as defined in the specification." Office Action at page 6. The Office then goes on to discuss the so-called Wands factors in support of its assertion, arguing that "the specification is silent concerning the parameters which constitute an 'immune response' i.e., development of humoral and/or cellular immune response to the antigen administered." Office Action at page 7. On this basis alone, the Office asserts that the skilled artisan would need to practice undue experimentation to make and use the invention as claimed. Applicants respectfully traverse.

Applicants have disclosed and claimed methods for delivering compositions containing multiple *M. tuberculosis* antigens to a subject in such a way as to stimulate humoral and/or cytotoxic immune responses. By their express showings in Example 2, applicants have demonstrated that their claimed method can be used to deliver numerous such antigens to mammalian subjects, and that the vaccinated subjects were protected against either actual infection or progression of tuberculosis disease as indicated by either survival after infection challenge, or reduction in physiological damage associated with

tuberculosis infection. Applicants claim that this is due to the generation of the desired immune response in the vaccinated animals.

The Office has not disputed the underlying truth of the experimental results detailed in Example 2, and there is simply no reason of record to believe that delivery of antigens using applicants' method would not bring about such immune responses. Thus, the Office cannot point to any substantive reason to doubt the objective truth of applicants' enabling disclosure. Section 112 requires nothing more than objective enablement. Accordingly, to support the present rejection for lack of enablement, it is incumbent upon the Office to explain why the objective truth of applicants' disclosure is doubted and to back up such assertions with acceptable objective evidence or reasoning in support thereof. No such objective evidence has been tendered. Since the Office has not provided any express evidence that applicants' claimed methods would not produce the desired immune response, there is no valid burden upon applicants to provide additional evidence, such as other working examples or the like, to supplement their presumptively correct supporting disclosure. *See, e.g., In re Marzocchi*, 169 U.S.P.Q. 367 (CCPA 1971).

For all of these reasons, then, the rejection of claims 7-49 under 35 U.S.C. §112, first paragraph, is improper. Reconsideration and withdrawal is thus respectfully requested.

The Office then goes on to assert that the specification, "while enabling for alterations in weight, bacterial load, and tissue pathology in guinea pigs, does not reasonably provide enablement for eliciting an immune response in humans." Office Action at page 7. The Office then goes on to support its' position citing a review from 1989 (Evaluation of the Protective Potency of New Tuberculosis Vaccines," *Review of Infectious Diseases*, v.11, Suppl. 2, pages S484-S490, March-April 1989), and noting "there are no examples of human subjects." Office Action at page 9. The Office then concludes "based

on a lack of success in humans concerning tuberculosis vaccines and a lack of correlation of success in animal models [the skilled artisan would need to practice undue experimentation to make and use the invention as claimed]." Office Action at page 9. Applicants respectfully traverse.

Initially, applicants draw the Office's attention to the specification at page 33, lines 13-22, where it is disclosed that the guinea pig challenge model used in the study of Example 2 is well established in the field and used in studies of events in infected humans who follow similar patterns, citing Baldwin et al. (1998) *Infection and Immunity* 66:2951-2959. Applicants submit that this reference represents a much more contemporary view of the skilled artisan's perception of animal models for use in studying tuberculosis than the Office's 1989 abstract review. It is also clear that both applicants and Baldwin et al. take an entirely different view than the Office on the strength of the guinea pig animal model.

Applicants submit that their experimental (working model) showing in Example 2 is more than sufficient to meet their burden under Section 112. What the Office seems to suggest is, absent actual human clinical data, applicants' specification cannot be enabling for human applications. This apparent requirement that applicants must have actually carried out human studies is improper and not supported by any statutory rule. This is because were such a requirement actually valid, it would discourage inventors from disclosing and teaching their discoveries for the public's benefit until an exhaustive experimental study into any and all possible embodiments had been completed, which discouragement is antithetical and in direct contradiction of the guiding principals underlying Section 112. See, e.g., *Rohm & Hass Co. v. Dawson Chemical Co.*, 217 USPQ 515, 563-564 (S.D. Tex. 1983), *rev'd on other grounds*, 220 USPQ 289 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984).

Applicants have provided sufficient enabling disclosure for their recited methods and have even provided numerous working examples of the use of various nucleic acid compositions in an art-accepted animal model. The Office has not tendered any plausible scientific basis for why the guinea pig animal model would not be predictive for humans, and there is frankly no valid reason to doubt that applicant's methods will work for their intended purpose in humans. The Office has thus failed in its burden to provide a reasonable basis to question the enablement that applicant has provided *In re Wright*, 27 USPQ2d 1510 (Fed. Cir. 1993). In fact, the only way to supplant applicants' presumptively correct disclosure (supported by multiple working examples) is to completely ignore or discount the experimental showing that applicants have provided. This is improper since applicants' disclosure must be viewed as in compliance with the enablement requirement of Section 112, unless there is reason to doubt the objective truth thereof. *In re Marzocchi*, 169 USPQ 367 (CCPA 1971).

For all of the foregoing reasons, then, the rejection of claims 1-49 under 35 U.S.C. §112, first paragraph, is improper. Reconsideration and withdrawal of the rejection is thus earnestly solicited.

Finally, claims 8-13, 16-21, 30-35 and 42-47 stand rejected under 35 U.S.C. §112, first paragraph, as nonenabled. Here, the Office acknowledges that applicants have demonstrated their prime/boost methods using BCG as the secondary boosting composition (Office Action at page 9), but asserts that other boosting agents are not enabled. The Office then goes on to discuss the Wands factors in support of its assertion, arguing that "the specification is silent concerning the other claimed 'boosting' compositions." Office Action at page 10. On this basis alone, the Office asserts that the skilled artisan would need to practice undue experimentation to make and use the invention as claimed. Applicants respectfully traverse.

As noted above, applicants have provided sufficient enabling disclosure for their recited methods. With respect to the methods that entail the use of a boosting composition, applicants have shown an exemplary combination entailing the use of a BCG secondary composition, and this showing has been acknowledged by the Office. The Office has not tendered any plausible scientific basis for why applicants' exemplary prime/boost compositions would not be predictive for other secondary compositions, and there is frankly no valid reason to doubt that applicant's other recited combinations will indeed work. The Office has thus failed in its burden to provide a reasonable basis to question the enablement that applicant has provided *In re Wright*, 27 USPQ2d 1510 (Fed. Cir. 1993). In fact, the only way to supplant applicants' presumptively correct disclosure is to completely ignore or discount the experimental showing that applicants have provided. This is improper since applicants' disclosure must be viewed as in compliance with the enablement requirement of Section 112, unless there is reason to doubt the objective truth thereof. *In re Marzocchi*, 169 USPQ 367 (CCPA 1971).

Accordingly, the rejection of claims 8-13, 16-21, 30-35 and 42-47 under 35 U.S.C. §112, first paragraph, is improper. Reconsideration and withdrawal of the rejection is thus respectfully requested.

The Rejections under 35 U.S.C. §103(a):

Claims 7-11 and 15-19 stand were rejected under 35 U.S.C. §103(a) as unpatentable over Lowrie. In particular, the Office asserts "Lowrie et al. teach a method using plasmids comprising polynucleotides encoding various *M. tuberculosis* antigens." However, the Office acknowledges that "Lowrie do not teach a composition ... comprising ≥2 polynucleotides or a composition of multiple plasmids" (Office Action at page 11), but then points to a passing statement appearing at page 837, column 2, lines 11-15 of Lowrie that states "a

vaccine that gives protection equal to BCG by endogenous expression of only a few proteins will leave the majority of the species specific antigens available for diagnostic tests." The Office then concludes that it would have been obvious to arrive at applicants' recited methods. Applicants respectfully traverse.

Section 2143 of the M.P.E.P. sets forth the following three basic requirements for *prima facie* obviousness: (1) there must be some suggestion or motivation to modify or combine the references; (2) there must be a reasonable expectation of success for the modification and/or combination; and (3) the prior art reference must teach or suggest all the claim limitations. When assessing these issues, (1) the claimed invention must be considered as a whole; (2) the references must be considered as a whole and must suggest the desirability of making the combination; (3) the references must be viewed without the benefit of impermissible hindsight; and (4) a reasonable expectation of success is the standard with which obviousness is determined. *Hodosh v. Block Drug Co., Inc.*, 229 USPQ 182, 187, n.5 (Fed. Cir. 1986). Applicants submit that the Office has failed to satisfy these criteria, and has thus failed to establish *prima facie* obviousness over Lowrie.

Applicants respectfully submit that the Office seems to have premised its entire rejection on the basis of one possible interpretation of an entirely ambiguous statement taken out of context from the rest of the publication. This interpretation is based upon a hindsight reconstruction of applicant's recited methods, not on any fair reading of Lowrie. What Lowrie did discuss is that a number of discrete (5) mycobacterial antigens were screened as DNA vaccines, and that three of them provided significant protection against tuberculosis disease. See Lowrie, page 837, column 1. Although it would have been, in theory, perfectly possible for Lowrie et al to combine two or more antigens in their study, they neither did this nor suggested that this should be done. The document is entirely silent on the idea of providing a

vaccine composition containing multiple tuberculosis antigens. In fact, Lowrie showed that numerous single antigen vaccines provided "significant protection." Accordingly, this showing would suggest an entirely opposite and perhaps more plausible interpretation of the Office's cited passage, where Lowrie are suggesting that a number of different antigen systems could be used to vaccinate different individuals in a population, facilitating broad spectrum diagnostic testing in the vaccinated population.

The only real way to arrive at the Office's suggested interpretation is to use applicants' specification as a template. This is of course not permissible. Accordingly, the Office has failed to establish its *prima facie* showing of obviousness since Lowrie fails to teach or suggest all of applicants' recited claim limitations. This is because when Lowrie is properly considered as a whole, it simply does not suggest the desirability of making the combination that has been suggested by the Office.

For all of the foregoing reasons, then, the rejection of claims 7-11 and 15-19 under 35 U.S.C. §103(a) is improper. Reconsideration and withdrawal of the rejection is thus earnestly solicited.

Claims 23, 25-33 and 37-45 stand rejected under 35 U.S.C. §103(a) as unpatentable over the combination of Lowrie in view of Sanford. In particular, the Office asserts that Lowrie "teaches a method using plasmids comprising polynucleotides encoding [single] antigens," and, although Lowrie et al. "do not teach a composition comprising ≥2 polynucleotides or a composition of multiple plasmids ... Lowrie do suggest multiantigen plasmid vaccines." Office Action at page 12, Sanford is cited for teaching transdermal delivery systems, and the Office thus concludes that it would have been obvious to arrive at applicants' recited methods. Applicants respectfully traverse.

As discussed above, the primary reference to Lowrie fails to teach or suggest applicants' recited multiple antigen constructs. The secondary

reference to Sanford does not provide the missing teaching or suggestion. Accordingly, the Office has failed to establish a *prima facie* showing of obviousness over its proposed combination since the combination and each component thereof fails to teach or suggest all of applicants' recited claim limitations. Accordingly, the rejection of claims 23, 25-33 and 37-45 under 35 U.S.C. §103(a) is improper. Reconsideration and withdrawal is thus respectfully requested.

CONCLUSION

Applicants respectfully submit that the claims as now pending define an invention which complies with the requirements of 35 U.S.C. § 112 and which is novel and nonobvious over the art. Accordingly, allowance is believed to be in order and an early notification to that effect is earnestly solicited. Applicants further ask that, should the Examiner note any minor remaining issues that may be resolved with a telephone call, that he contact the undersigned in the UK at +44 1865 332 600.

Respectfully submitted,

Date: 20 May 2002

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